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CUSPA

TECHNOLOGY LAW ASSOCIATES
11820 SW 107TH AVENUE • MIAMI, FLORIDA 33176
PHONE (786) 242-9349 • FAX (786) 242-9349

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TO: Examiner Richard Schnizer FROM: Yi Li

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Dear Examiner Schnizer:

Attached is the draft Appeal Brief for our conference call on Tuesday, Feb. 4, 2003 (8:30AM). Please provide a copy to Examiner Brian Stanton and anyone else that will participate.

If you have any questions, please call me at (305) 776-2430 (cel).

Thank you.

Yi

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Atty Docket: 99,001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT AND INTERFERENCES

In re Application of:	)	Date: February 1, 2003
Hai Xing Chen	)	
Serial No.: 09/253,573	)	Group Art Unit: 1635
Filed: February 19, 1999	)	Examiner: Richard A. Schnizer
For: A Method For Production And Delivery of A Protein in Vivo	)	**DRAFT**

Commissioner for Patents
Box AF
Washington, D.C. 20231

Sir:

APPEAL BRIEF

Mitchell E. Alter
Patent Attorney for Appellant
Registration No. 28,684
AND
Yi Li
Patent Agent for Appellant
Registration No. 44,211
CUSPA Technology Law Associates
11820 SW 107TH Avenue, Miami, Florida 33176
Telephone (786) 242-9349 • Fax (786) 242-9349

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LIST OF LEGAL AUTHORITIES

In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)

PPG Indus., Inc. v. Guardian Indus. Corp., 75 F.3d 1558, 37 USPQ 2d 1618, (Fed. Cir. 1996)

In re Goodman, 11 F.3d 1046, 29 USPQ 2d 2010 (Fed. Cir. 1993)

Raytheon Co. v. Roper Corp, 724 F.2d 951, 220 USPQ 592 (Fed. Cir. 1983), *Cert. Denied*, 469 U.S. 835 (1984)

Enzo Biochem Inc. v. Calgene Inc., 188 F.3d 1362, 52 USPQ2d 1129 (Fed. Cir. 1999)

National Recovery Techs., Inc. v. Magnetic Separation Sys., Inc., 166 F.3d 1190, 49 USPQ2d 1671 (Fed. Cir. 1999)

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APPELLANT'S APPEAL BRIEF

This is an appeal from the Examiner's Final Rejection of July 15, 2002 in which all claims then pending in the above referenced application (i.e. Claims 1, 2, 6-8, 11, 12 and 14) were finally rejected under 35 U.S.C. §112, first paragraph.

1. REAL PARTY IN INTEREST

This patent application was originally assigned by the Inventor, Dr. Hai Xing Chen, to ACGT Corporation, the present assignee and real party in interest in this appeal. Dr. Chen is the President of ACGT Corporation.

2. RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences known to Appellant, the Appellant's legal representatives or Assignee which will directly affect or be directly affected by or have a bearing on the Board's Decision in the pending appeal.

3. STATUS OF CLAIMS

The present application originally contained Claims 1-43. Appellant elected to prosecute Claims 1-29 and cancelled Claims 30-43 in a Response to Requirement For Restriction dated April 20, 2000. Claims 9 and 22-23 were cancelled by Amendment dated April 24, 2002. Claims 3-5, 10, 13, 15-21 and 24-29 were cancelled by Amendment After Final dated November 15, 2002. Currently, Claims 1, 2, 6-8, 11, 12 and 14 are pending. All claims are method claims, and only Claim 1 is presented in independent form. No claim has been allowed.

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4. STATUS OF AMENDMENTS

After the Final Rejection of Claims 1-8, 10-21 and 24-29, Appellant filed an Amendment After Final Rejection deleting Claims 3-5, 10, 13, 15-21 and 24-29 to reduce the pending rejections to a single issue for consideration by the Examiner and present reasons for patentability. By an Advisory Action of December 17, 2002, Appellant was advised that the Amendment after Final Rejection was entered and considered, but that Claims 1, 2, 6-8, 11, 12 and 14 remained rejected.

5. SUMMARY OF THE INVENTION

The invention underlying this appeal addresses the technical problems of providing a method for production and delivery of a protein in vivo. Appellant's claimed invention uses a native promoter to produce a non-hemoglobin protein only in the progenitor cells of red blood cells, and uses the produced red blood cells to deliver the protein into the bloodstream through rupture of the red blood cells.

Appellant's claimed invention is a separate and distinct invention from a method of gene therapy. More specifically, Appellant's claimed invention is not a method of treating diseases using gene therapy. Furthermore, although the present invention can potentially be employed in disease treatment, Appellant's claimed invention as defined by the claims is not, nor ever intended to be, a gene therapy method.

The claimed invention comprises inserting into a vector a promoter which is active only in progenitor cells of red blood cells, and a gene encoding a protein which is non-native to red blood cells, wherein said promoter and said gene are operably linked; collecting an amount of progenitor cells of red blood cells from a mammal; transfecting said progenitor cells of red blood cells in vitro with said vector containing said promoter and said gene; introducing the transfected progenitor cells of red blood cells back to said mammal, wherein the transfected progenitor cells of red blood cells produce altered red blood cells containing said protein which is non-native to red blood cells in vivo in said mammal, and wherein said protein which is non-native to red blood cells is contained only in said alt r d red blood cells, and thereafter said protein which is non-

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nativ to red blood cells is released into a bloodstream of said mammal through rupture of said altered red blood cells.

6. ISSUE

Appended Claims 1, 2, 6-8, 11, 12 and 14 which are on Appeal have been rejected under 35 USC §112, first paragraph, for lack of enablement.

The Examiner argued this rejection in the first Office Action dated October 22, 1999 (Paper No. 3). The rejection was traversed by Appellant's response to the Office Action dated April 20, 2000 (Paper No. 6). The Examiner withdrew the rejection in the second Office Action dated July 17, 2000 (Paper No. 7) stating that Appellant made the statement in prosecution of the claims that "the claimed invention is not intended to be used for gene therapy". Appellant was particularly concerned with prosecution history estoppel and therefore respectfully informed the Examiner in the response to the second office action that Appellant did not make any such disclaimer. Appellant's response to the rejection was that the claimed invention was directed to a method for in vivo producing and delivering a protein to the bloodstream, which the Examiner had previously noted was enabled by the Specification.

The Examiner subsequently argued and maintained the lack of enablement rejection in the third Office Action dated October 25, 2001 (Paper No. 14) and fourth Office Action Final dated July 15, 2002 (Paper 17). In the Advisory Action dated December 27, 2002 (Paper 21), the Examiner stated that, "Appellant has failed to point to any purpose for production and delivery in vivo other than gene therapy, and the specification fails to teach one." The Examiner raised the a utility issue of whether there is any purpose for production and delivery other than gene therapy, and reasoned that if there are no other utilities, then the claims must be interpreted and restricted to being a gene therapy method.

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The following issue is presented for review by the Board of Patent Appeals and Interferences:

> Is it appropriate for the Examiner to reject method claims for producing and delivering protein in vivo under 35 USC §112, first paragraph, by arguing that there is a lack of enablement for the use of the protein product produced for gene therapy?

Quite candidly, the Board will find that Appellant's representatives wrote the present patent specification with much enthusiasm about the potential of the claimed method of producing and delivering protein in vivo being useful in subsequent gene therapy. However, neither Appellant nor Appellant's representative ever intend that the claimed method be a disease treatment. In fact, Appellant's representatives were well aware of the enablement problem with patent application claims to gene therapy and foreign patent laws prohibition against claims to treatment of diseases. Therefore, Appellant's representatives' position had been and continues to be to maintain that the production and delivery of protein in vivo is itself a sufficient utility, which is enabled by the specification, and that no further enablement of gene therapy is necessary. Notwithstanding the inappropriateness of the Examiner's reasoning of the rejection of the claimed method on the basis of lack of enablement for the specific use of the product produced for gene therapy, Appellant will present in this Brief on Appeal additional information demonstrating that in vivo production of protein has utility beyond gene therapy.

7. GROUPING OF CLAIMS

For the purpose of this appeal only, Appealed Claims 1, 2, 6-8, 11, 12 and 14 may be grouped together and it may be presumed that in regards to patentability that the Appealed claims stand or fall together.

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8. ARGUMENT

Appealed Claims 1, 2, 6-8, 11, 12 and 14 stand rejected under 35 U.S.C. §112, first paragraph. The Examiner supports this rejection by finding that the claimed invention encompasses gene therapy which is not enabled by the present specification. The Examiner used the factors enunciated in In re Wands, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988) to determine that the specification's disclosure is insufficient such that undue experimentation would be required to practice gene therapy. This rejection is respectively traversed.

The dispositive issue in the present application is "What is the claimed invention?" Appellant maintains that as defined, the present claimed invention is a method for producing and delivering protein in vivo. More specifically, the method comprises inserting into a vector a promoter which is active only in progenitor cells of red blood cells, and a gene encoding a protein which is non-native to red blood cells, wherein said promoter and said gene are operably linked; collecting an amount of progenitor cells of red blood cells from a mammal; transfecting said progenitor cells of red blood cells in vitro with said vector containing said promoter and said gene; introducing the transfected progenitor cells of red blood cells back to said mammal, wherein the transfected progenitor cells of red blood cells produce altered red blood cells containing said protein which is non-native to red blood cells in vivo in said mammal, and wherein said protein which is non-native to red blood cells is contained only in said altered red blood cells, and thereafter said protein which is non-native to red blood cells is released into a bloodstream of said mammal through rupture of said altered red blood cells.

Appellant's claimed invention is not a method of using proteins produced in vivo to treat diseases. Furthermore, although the present invention can be used for facilitating disease treatment as apparent to one skilled in the art, Appellant claimed invention as defined by the claims is not, nor ever intended to be, a gene therapy method.

Whether a claim is enabled under 35 U.S.C. 112, paragraph 1 is a question of law, although based upon underlying factual findings. See PPG Indus., Inc. v. Guardian

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Indus. Corp., 75 F.3d 1558, 1564, 37 USPQ 2d 1618, 1623 (Fed. Cir. 1996); In re Goodman, 11 F.3d 1046, 1049-50, 29 USPQ 2d 2010, 2013 (Fed. Cir. 1993).

The first paragraph of 35 U.S.C. 112 states:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The present rejection is based upon the Examiner's definition of what subject matter is encompassed by the claims and not on the Specification and plain meaning of the claim words. The Examiner has attempted to expand the claims to encompass gene therapy because it is mentioned in the Specification. However as held in Raytheon Co. v. Roper Corp, 724 F.2d 951, 957, 220 USPQ 592, 597 (Fed. Cir. 1983), *Cert. Denied,* 469 U.S. 835 (1984), "That claims are interpreted in light of the specification does not mean that everything in the specification must be read into the claims."

The Examiner has failed to point out any particular claim elements, which are broader than a method of producing a protein only in the progenitor cells of red blood cells, and delivering produced protein into bloodstream by rupture of the red blood cells such that the claim elements are not enabled. Enzo Biochem Inc. v. Calgene Inc., 188 F.3d 1362, 1371, 52 USPQ2d 1129 (Fed. Cir. 1999).

In addition, the Examiner has failed to point out any inconsistency in the plain meaning of the claim terms to indicate that the claim terms are broader than a method of producing a protein only in the progenitor cells of red blood cells, and delivering produced protein into bloodstream by rupture of the red blood cells such that the claim terms are not enabled. National Recovery Techs., Inc. v. Magnetic Separation Sys., Inc., 166 F.3d 1190, 1194, 49 USPQ2d 1671, 1674 (Fed. Cir. 1999).

Appellant is only responsible for enablement of the disclosed method within the scope defined by the claims, not beyond the scope of the claims. As Examiner previously stated on page 4, line 6 of the first Office Action, the present invention is "enabling for delivery of a protein to the blood in vivo". That is pr cisely the claimed

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invention. Now however, the Examiner has withdrawn from this position in the fourth Office Action in order to support his enablement r jection for gene therapy.

Appellant intentionally avoided the therapeutic enabling issue by employing an approach that has been readily accepted, as shown in the primary reference, Hollis et al., which was used by the Examiner in further claim rejections. In the Hollis et al. reference, as well as, other protein expression patents, each uses the same strategy of claiming the expression or production of proteins rather than a specific gene therapy protocol. For example, Hollis et al recites purification of recombinant proteins. Still others adopt similar ways to claim either expression or production of proteins rather than the gene therapy for which the proteins would be used. Appellant has adopted this same approach by claiming the production and delivery of proteins rather than a method how to use the produced protein for the purpose of gene therapy. Gene therapy itself is a separate and very complex scientific subject that needs to be specifically addressed depending on each specific disease, organ involved and protein intake mechanism involved, regardless how the desired protein is produced.

Appellant has never claimed gene therapy. In fact, in the Background of the Invention, Appellant pointed out that gene therapy comprises many components necessary to obtain a specific gene therapy and each component has many variables. Therefore, it is apparent to the Appellant, the Examiner and those skilled in the art that each component, as well as, the precise gene therapy protocol would be new inventions. However, using the Examiner's unduly expanded interpretation of the claims, the Examiner is in effect denying Appellant's ownership of the claimed method of protein production and delivery just because the method can potentially be used in a therapeutic procedure. More specifically, if a precise gene therapy protocol was invented which uses Appellant's claimed protein production and delivery method, then the Examiner's position denies Appellant's inventive rights to Appellant's claimed invention. It is untenable of the Patent Office to refuse granting Appellant a patent on Appellant's discovered method merely because the discovered method is susceptible of further uses. It would be patently unjust to require an Applicant to delay seeking patent protection on one method of protein production and delivery until after a specific gene therapy has been discovered and has proven clinical use.

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The Examiner's subjective view is not consistent with objective views that Appellant's claimed method of protein production and delivery is separate from an invention directed to the use of the protein in a gene therapy method. It is readily understood that a process to make a product is separate from a process to use the product for a specific purpose. Appellant believes that the present situation can be analogous to Appellant claiming a method of producing time-release high potency Vitamin C tablets, but Appellant would not be responsible for any clinical use of the Vitamin C for treatment of diseases. Consequently, Appellant maintains that Appellant should not be required to provide an enablement for the separate invention of gene therapy.

The Examiner's rejection is simply unfair and not logical to promoting the useful arts. Appellant maintains that he has complied with the requirements of 35 U.S.C. §112, first paragraph. Appellant's claimed invention has utility for producing and delivering proteins in vivo. The present Specification, page 6, provides a host of utilities for Appellant's claimed invention. More specifically:

> One object of the present invention is to provide a non-tissue specific method that utilizes suitable host cells for synthesis of proteins.
>
> Another object of the present invention is to specifically control the expression and production of proteins in the precursors of the red blood cells.
>
> An additional object is to utilize the non nucleated cell nature of the red blood cells to provide an environment that benefits the stability of the proteins after their production.
>
> Yet another object of the present invention is to bypass the secretion and exocytosis pathways for protein release from the manufacturing site.

Even given these utilities, the Examiner argues that none of them provide "reasons" for in vivo production and delivery of proteins as claimed and requires that "the specification must enable the practice of gene therapy of the broad range of disease set forth in the specification." However as previously cited, Raytheon Co. v.

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Roper Corp, *ibid*, holds that claims are interpreted in light of the specification does not mean that ev_rything in th specification must be read into th claims.

Moreover, even though the claimed invention has potential utility in gene therapy, Appellants should not be required to enable gene therapy. For example, the fact that a valve is used in an instrument does not mean that a claim of a new method of making the valve must be accompanied with an enabling disclosure of how to make the instrument. All that is required is that the method of making the valve be described and enabled.

As previously mentioned, the Examiner initially indicated that the invention was enabling for the production and delivery of protein in vivo. But now, the Examiner has not provided any reason why the claimed invention is not separately enabled for the production and delivery of protein in vivo, except that the claimed production and delivery of protein in vivo can be used in gene therapy and gene therapy is not enabled by the specification. Appellant maintains the two are separate in nature and should not be construed as one invention. Appellant is only obligated to enable the claimed invention but not the other.

Notwithstanding the inappropriateness of the Examiner's reasoning of the rejection of the claimed method on the basis of lack of enablement for the specific use of the product produced for gene therapy, Appellant presents in this Brief on Appeal additional information demonstrating that in vivo production of protein has utility beyond gene therapy. For example, it is known to one skilled in the art at the time of filing of the instant application that a protein produced in mammals can be harvested, purified, and then used as a protein supply for medical treatment in a similar manner to a medication, which is outside of the scope of gene therapy. In the present case, the mammalian body wherein the protein is produced in vivo, and delivered to a convenient harvesting site, for instance the bloodstream, is utilized as a "bioreactor" for manufacturing a desired protein which otherwise is difficult to obtain by other means.

A suitable example of bioreactor protein production is the production of human Alph-1 antitrypsin (AAT) in transgenic animals for treating AAT deficiency patients. AAT is a protein normally made in human liver. From the liver, AAT is released into the bloodstream, to travel to the lungs where it protects lung tissue from the harmful effects

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of neutrophil elastase. AAT deficiency is an inherited disorder. Because the AAT defici ncy patients lack the ability to produce sufficient AAT, or not produce it at all, it can lead to emphysema at a young age.

Pharmaceutical Proteins Limited (PPL), Edinburgh, United Kingdom, demonstrated in early 1990 that human AAT can be produced with an adequate yield in transgenic sheep and harvested from the milk of these animals. The human AAT purified from the milk of these transgenic animals has biological activity indistinguishable from human plasma derived material *(Biotechnology (NY) 1991 Sept., 9(9):830-4).* PPL Therapeutics and Bayer Corporation later launched clinical trials, which used the AAT produced by transgenic sheep to treat AAT deficiency patients (www.bayerbiologicals.com). The AAT in an aerosol formulation is delivered directly to the patients' lungs via an inhalation system. In another application, PPL also concluded its Phase II clinical trial in November 1998 for using three dosages of AAT to treat cystic fibrosis patients (www.ppl-therapeutics.com).

It is apparent that using the method of Appellant's claimed invention the AAT protein can be produced in the red blood cells via the control of the hemoglobin promoter and delivered into blood stream in a human body. However, using the method of Appellant's claimed invention human AAT protein can also be produced in the red blood cells and delivered into the bloodstream in sheep or other mammals, and then harvested and used as a protein supply for medical treatment of AAT deficiency patients, in a similar manner to PPL Therapeutics' approach. The difference between PPL Therapeutics' method and Appellant's claimed invention is in the method of in vivo protein production. PPL Therapeutics uses transgenic animals to produce the protein in mammary glands and Appellant's claimed method uses a non-transgenic animal to produce the protein in red blood cells of the mammal.

Appellant respectfully points out that Appellant's claimed invention is a method of producing and delivering protein in vivo, not how to use the produced protein. Gene therapy is only one possible approach to utilize the produced protein. It is important to understand that the protein produced by Appellant's claimed method can be utilized by means other than gene therapy.

Therefore, Appellant maintains that the pending application is in complianc with

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the requirements of 35 U.S.C. §112, first paragraph.

9. CONCLUSION

Accordingly, for all the reasons expressed above, the final rejection of the Claims on Appeal should be reversed by the Board and the application should be allowed to issue.

Date of Signature

By:_____
Mitchell E. Alter
Registration No. 28,684
Attorney for Appellant
(305) 491-6528

Date of Signature

By:_____
Yi Li
Registration No. 44,211
Agent for Appellant
(305) 776-2450

Address correspondence to:

CUSPA Technology Law Associates
11820 SW 107 Avenue
Miami, Florida 33176
Fax : (786) 242-9349
Telephone: (786) 242-9349

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APPENDIX A – CLAIMS ON APPEAL

1. A method for producing and delivering protein in vivo comprising the steps of:

(a) inserting into a vector a promoter which is active only in progenitor cells of red blood cells, and a gene encoding a protein which is non-native to red blood cells, wherein said promoter and said gene are operably linked;

(b) collecting an amount of progenitor cells of red blood cells from a mammal;

(c) transfecting said progenitor cells of red blood cells in vitro with said vector containing said promoter and said gene;

(d) introducing the transfected progenitor cells of red blood cells back to said mammal, wherein the transfected progenitor cells of red blood cells produce altered red blood cells containing said protein which is non-native to red blood cells in vivo in said mammal, and wherein said protein which is non-native to red blood cells is contained only in said altered red blood cells, and thereafter said protein which is non-native to red blood cells is released into a bloodstream of said mammal through rupture of said altered red blood cells.

2. The method of Claim 1 further comprising inserting an enhancer in said vector.

6. The method of Claim 1 wherein said vector is a viral vector.

7. The method of Claim 6 wherein said viral vector is selected from the group consisting of a retroviral vector, an adenoviral vector and a lentiviral vector.

8. The method of Claim 1 wherein said progenitor cells of red blood cells are stem cells.

11. The method of Claim 1 wherein said protein is a member selected from the group consisting of an antibody, enzyme, cofactor, interferon, and hormone.

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12. The method of Clam 1 wherein said protein is a peptide.

14. The method of either one of Claims 11 or 12 wherein said protein which is non-native to red blood cells is a fusion protein.

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